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Recommendations

EULAR recommendations for the management of systemic lupus erythematosus with kidney involvement: 2025 update

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ABSTRACT

Objectives: The objective of this study was to update the 2019 European Alliance of Associations for Rheumatology (EULAR)/ European Renal Association/European Dialysis Transplantation Association (ERA-EDTA) recommendations for the management of systemic lupus erythematosus (SLE) with kidney involvement, taking into consideration emerging evidence and recent developments in the field.

Methods: We recruited an international Task Force of experts and followed the EULAR standard operating procedures. We performed systematic literature research (period January 2019 to March 2024), followed by the modified Delphi method, to form questions, elicit expert opinions, and reach consensus. The new evidence was examined, taking into consideration previous updates.

Results: The Task Force agreed on 4 overarching principles and 13 recommendations, which were also evaluated for their feasibility and impact on clinical care. These concern the use of kidney biopsy for diagnosis; targets of therapy and treatment milestones; immunomodulatory therapy with antimalarials, glucocorticoids, immunosuppressives (mycophenolate, cyclophosphamide, and calcineurin inhibitors), and biologics (belimumab, obinutuzumab, and rituximab); nonimmune therapy (kidney protection, vaccinations, cardiovascular, and bone protection); family planning; and management of kidney failure. Guidance on single-agent or early combination immune therapy, glucocorticoid tapering and withdrawal, duration of immune therapy, and treatment of refractory disease is provided.

Conclusions: The updated EULAR recommendations provide evidence- and expert-based consensus on the management of SLE with kidney involvement, adjusted for severity, and taking into consideration long-term efficacy, safety, cost, and local availability of drugs.

INTRODUCTION

Kidney involvement affects a significant proportion (20%-60%, depending on racial/ethnic background) of patients with systemic lupus erythematosus (SLE) and has a profound impact on prognosis [1]. Despite therapeutic advances, up to 15% of patients still reach kidney failure [2]. Moreover, 40% to 60% of patients with lupus nephritis (LN) develop chronic kidney disease (CKD), associated with substantial morbidity, especially cardiovascular.

The European Alliance of Associations for Rheumatology (EULAR), in conjunction with the European Renal Association/ European Dialysis Transplantation Association (ERA/EDTA), has published recommendations for the management of LN in 2012 [3], which were updated in 2019 [4]. Recently, a EULAR update of the management recommendations for general SLE was published, which included individual statements for treatment of kidney disease [5]. Nevertheless, novel advances on LN treatment, with the approval of belimumab and voclosporin for 'all patients with active LN', as well as more recently, the successful phase 3 trial of obinutuzumab, have provided physicians and patients with an expanded armamentarium of agents, necessitating an update of the specific recommendations for kidney involvement in SLE.

METHODS

We followed the EULAR standard operating procedures (SOPs) [6] and the Appraisal of Guidelines Research and Evaluation (AGREE II) instrument [7]. Following approval by the EULAR Quality of Care Subcommittee and the EULAR Council, the convenor (DB) assembled a multidisciplinary Task Force of 17 rheumatologists, 8 nephrologists, 1 paediatric rheumatologist, 1 allied health professional, and 2 patient representatives; among them, there were also 2 methodologists (GB and CAS), 2 fellows responsible for the systematic literature reviews (SLR) (AF and MK), and 2 members representing the EMerging EUlar NETwork (EMEUNET) (A-VM and CSS). Importantly, to accomplish a wider representation, this Task Force included experts outside Europe, specifically 3 from the Americas (1 from the

USA [RF], 1 from Canada [DDG], and 1 from Argentina [AM]), and 2 from Asia (CCM and YT). All members completed a conflict of interest form.

Following the assembly of the Task Force, an outline of the proposed methodology, a set of the main research questions, and the respective Population, Intervention, Comparison, and Outcomes (PICOs) were circulated among the panelists for their comments, edits, and possible additions. This process resulted in 6 different domains for the SLR: (1) indications for diagnostic kidney biopsy, (2) immune treatment of LN, (3) nonimmune treatment of LN, (4) targets of treatment, (5) duration of treatment, and (6) role of repeat kidney biopsy. More details on specific PICO questions and subquestions are provided in a dedicated manuscript regarding the methodology and results of the SLR [8]. Briefly, separate PICOs and search strings were developed for each domain, resulting in 6 different SLRs. The 2 fellows, supervised by the methodologists, searched MEDLINE and EMBASE for English language studies covering the period between January 2019 and end of March 2024 (the 2019 recommendations on LN had included papers until December 2018). Additional relevant articles identified through manual searches of reference lists from the retrieved publications were also included. Evidence related to the paediatric age groups was included in this process, supported also by the international paediatric SHARE LN recommendations [9]. Risk of bias assessment was performed using the Cochrane Risk of Bias tool [10] and Newcastle-Ottawa scale for randomised controlled trials (RCTs) and observational studies [11], respectively. The final level of evidence (LoE; scale: 1-4) and grading of recommendations (scale: A [highest] to D [lowest]), according to the Oxford Centre for Evidence-Based Medicine definitions [12], considered also the body of evidence that had informed the 2019 EULAR/ERA-EDTA recommendations.

The results of the SLRs were presented in detail to the members of the Task Force during a teleconference in September 2024, held virtually to facilitate the attendance of the international Task Force members. During a second face-to-face meeting (October 2024), a summary of the SLR results and an initial draft of the statements/recommendations were presented for discussion. Following open deliberations during this meeting, the statements were edited, and their final form was voted on by Task Force members present in the meeting. In view of the imminent publication of the phase 3 RCT of obinutuzumab, the Task Force decided to delay finalising the recommendations until publication of this study. Once this study was published and evaluated, obinutuzumab was added in 2 recommendations, and a second round of voting took place in February 2025 regarding only these 2 recommendations. Following finalisation, all Task Force members were asked to also provide their level of agreement with each recommendation.

Importantly, the 2019 recommendations for LN included a total of 41 different statements/recommendations, which belonged to 10 different domains (investigation of patient with suspected LN, pathological assessment of kidney biopsy, indications of immunosuppressive treatment, goals of treatment, initial treatment, subsequent treatment, nonresponding/refractory disease, adjunct treatment, monitoring and prognosis of LN, management of end-stage kidney disease in LN, antiphospholipid syndrome nephropathy, pregnancy, and management of paediatric LN). The current update aimed to comply with the new EULAR SOPs, which suggest a maximum of 15 bullet-point statements. To this end, some recommendations from the previous set were omitted and others were merged, while new recommendations were formulated. Due to these changes, for practical reasons, all overarching principles and individual recommendations of the current update are presented as new, even for recommendations that remain essentially unchanged. According to the EULAR SOPs, a recommendation was accepted if >75% of those present voted in favour. After the finalisation of the recommendation, each member of the panel was then asked to rate their level of agreement (LoA) for every statement on a 0 to 10 numerical rating scale (NRS, 10 being 100% agreement). To align with the most recent update of the EULAR SOPs, panelists were also asked to rate each recommendation on the following: (1) its feasibility for implementation in clinical practice, and (2) its impact on quality of care, both using a 0 to 10 NRS. The Task Force selected 3 recommendations with the best balance between feasibility and impact to develop quality indicators for future implementation.

RESULTS

The aforementioned procedure resulted in a final number of 4 overarching principles and 13 recommendations, shown in Table 1.

Overarching principles

The overarching principles refer to general information regarding diagnosis and management and reflect good clinical practice; thus, they are not accompanied by a supporting LoE. They nevertheless set the overall framework for the approach to the patients with SLE with kidney involvement and highlight the importance of multidisciplinary assessment and shared physician-patient decision-making.

A. *In patients with SLE, regular monitoring for signs and symptoms of kidney involvement, input from experts, and timely biopsy are essential to ensure optimal outcomes.*

Kidney involvement represents a critical event in the natural history of SLE, with profound prognostic repercussions. Therefore, physicians caring for lupus patients should have increased awareness of the development of signs of kidney disease (glomerular haematuria, proteinuria, decreasing glomerular filtration rate [GFR]). Although all lupus patients are at risk for LN, closer monitoring may be warranted in subsets with a particularly heightened risk, such as younger patients (paediatric and adults aged <30 years), males, or those with persistent serologic activity (hypocomplementemia and/or positive anti-DNA antibodies) [13]. A kidney biopsy assessed by an experienced nephropathologist, according to the 2003 International Society of Nephrology/Renal Pathology Society classification and its revisions, remains indispensable for the diagnosis of LN and the guidance of therapy [14,15]. With expanding options and increasing complexity of treatment, input from experts and specialised centres is considered essential to optimise prognosis.

B. *The management of patients with SLE with kidney involvement should align with the general recommendations for SLE, including treatment with hydroxychloroquine.*

The second overarching principle emphasises that kidney involvement is not a separate disease entity from SLE and should be managed according to general disease recommendations (most recent version published in January 2024) [5]. This notion is also highlighted in the title of the present

Table 1
EULAR recommendations for the management of patients with systemic lupus erythematosus and kidney involvement—2025 update

	Level of agreement	
Overarching principles	Mean (SD)	% with score ≥8
A. In patients with SLE, regular monitoring for signs and symptoms of kidney involvement, input from experts, and timely biopsy are essential to ensure optimal outcomes.	9.97 (0.19)	100
B. The management of patients with SLE with kidney involvement should align with the general recommendations for SLE, including treatment with hydroxychloroquine.	9.90 (0.41)	100
C. Kidney involvement in SLE carries the risk of progressive chronic kidney disease and is best managed with shared informed patient-physician decisions by rheumatology-nephrology interdisciplinary care teams, with regular assessment of risk factors for chronic kidney disease progression.	9.86 (0.44)	100
D. Management aims to prevent progression of chronic kidney disease and flares, address comorbidities, and improve health-related quality of life; both immunosuppressive therapy and nonimmune therapy, including kidney protection, are essential.	9.86 (0.35)	100
Recommendations		
1. Kidney biopsy is recommended in every patient with evidence of kidney involvement, especially in those with persistent proteinuria (≥0.5 g/24 h or urine protein-creatinine ratio [UPCR] ≥500 mg/g) (2b/B), glomerular haematuria (2b/C), and/or unexplained decrease in glomerular filtration rate (2b/C).	9.86 (0.44)	100
2. Treatment should aim for optimisation (preservation or improvement) of kidney function within 3 months, accompanied by a reduction in proteinuria of at least 25% by 3 months (2b/C), 50% by 6 months (2a/B), and a UPCR target <700 mg/g by 12 months (1b/B), and as low as possible afterwards.	9.83 (0.47)	100
3. For patients with active lupus nephritis, IV pulse methylprednisolone is recommended (2b/C), followed by oral glucocorticoids gradually tapered to ≤5 mg/d prednisone-equivalent by 4-6 mo (2b/C), and slowly withdrawn in patients with sustained complete renal response.	9.59 (0.68)	100
4. For patients with active lupus nephritis, especially those with poor prognostic factors, we recommend combination therapy of (a) mycophenolate or low-dose intravenous cyclophosphamide with belimumab (1b/A), (b) mycophenolate with a calcineurin inhibitor (voclosporin or tacrolimus) (1b/A), or (c) mycophenolate with obinutuzumab (1b/A). Alternative regimens include single-agent therapy with either mycophenolate (1a/A) or low-dose intravenous cyclophosphamide (1a/A).	9.59 (0.78)	96.5
5. In patients with rapidly progressive glomerulonephritis, a short course (6-7 monthly pulses) of high-dose intravenous cyclophosphamide can also be considered (1a/A).	8.97 (1.66)	93.1
6. Following renal response, treatment should continue for at least 3 years (2b/B); patients initially treated with mycophenolate alone (1a/A) or in combination with (1) belimumab (1b/A), (2) a calcineurin inhibitor (1b/A), or (3) obinutuzumab[a] should remain on these drugs; mycophenolate (1a/A) or azathioprine (1a/A) should replace cyclophosphamide for those initially treated with cyclophosphamide, alone or in combination with belimumab.	9.31 (1.14)	96.5
7. In patients with sustained complete renal response, gradual withdrawal of immunosuppressive and/or biologic therapy should be considered after 3 years of therapy following response, taking into consideration the risk for flare (2a/B).	9.31 (0.97)	93.1
8. For patients with persistently active or relapsing disease, switching among the aforementioned immunosuppressive (2b/B) and/or biologic drugs (2b/B) and referral to experts is recommended.	9.72 (0.59)	100
9. Repeat kidney biopsy should be considered, especially in cases of clinical uncertainty, to evaluate (1) response to treatment, (2) worsening of kidney-specific laboratory tests, or (3) contemplated withdrawal of immunosuppressive treatment (2b/B).	9.76 (0.58)	100
10. Nonimmune treatment with renin-angiotensin-aldosterone blockade (for patients with persistent proteinuria or arterial hypertension) (5/D), sodium glucose transporter 2 inhibitors (for stable patients with persistent proteinuria or estimated glomerular filtration rate <60 ml/min/m^2, or other risk factors for progressive chronic kidney disease) (5/D), statins (based on cardiovascular risk levels) (5/D), and/or bone protective agents (5/D) is recommended.	9.69 (0.71)	96.5
11. In patients with features of thrombotic microangiopathy (antiphospholipid syndrome nephropathy, thrombotic thrombocytopenic purpura-like, or complement-mediated hemolytic uremic syndrome), glucocorticoids (IV pulse methylprednisolone) (4/C), complement inhibitors (4/C), B-cell depleting agents (4/C), caplacizumab (4/C), plasma exchange (4/C), and/or anticoagulation (2b/C) should be considered.	9.52 (0.83)	96.5
12. In patients with inactive nephritis and adequately controlled extrarenal manifestations, pregnancy may be planned after preconception counselling, initiation of pregnancy-compatible medications, and regular multidisciplinary assessments (1b/A).	9.86 (0.35)	100
13. All methods of kidney replacement therapy can be used in patients with SLE; in those with clinically inactive extrarenal disease for at least 6 months, transplantation (including living donor and pre-emptive transplantation) should be considered (2b/C).	9.86 (0.52)	100

[a] Obinutuzumab was used for a maximum of 1 year (52 weeks) in the REGENCY trial; longer courses await further evaluation.
Levels of evidence according to the Oxford Evidence-based Medicine grading levels (https://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf).
NA, not applicable.

update, wherein 'lupus nephritis' has been substituted by 'kidney involvement', to denote that SLE is a systemic disease with various manifestations that may manifest over time, even in cases where nephritis can initially present as an organ-dominant disease. General management includes non-pharmacologic measures, including sun protection and smoking cessation, as well as the use of hydroxychloroquine (HCQ) [16]. In addition to its multiple benefits in SLE in general, HCQ has been associated with better outcomes specifically in LN [17].

C. *Kidney involvement in SLE carries the risk for progressive CKD and is best managed with shared informed patient-physician decisions by rheumatology-nephrology interdisciplinary care teams, with regular assessment of risk factors for CKD progression.*

The third principle emphasises the concept of CKD in the context of LN. CKD is defined as abnormalities of kidney structure or function present for at least 3 months with implications for health and is classified based on cause, GFR (G1-G5), and albuminuria (A1-A3) categories [18]. CKD is associated with multiple adverse outcomes, including cardiovascular morbidity, hospitalisations, and death. Kidney involvement in SLE accelerates the physiologic nephron loss that occurs with age, decreases the functional kidney reserve, and thus increases the risk for CKD development and progression [19]. This risk correlates strongly with a decreased GFR and an increased albumin-to-creatinine ratio (ACR), especially at levels <60 ml/min/m^2 and >30 mg/g, respectively [18,20]. Given the chronic nature of LN and that it often manifests in early adulthood, measures should be taken to delay the progression of

CKD. This is especially pertinent in childhood-onset disease, in view of the increased prevalence of kidney involvement and its associated severity in this age group [21].

As both rheumatologists and nephrologists are involved in the care of these patients, an interdisciplinary care team with input from both disciplines is important to ensure optimal outcomes. Age-, ACR-, and GFR-based charts for the estimated risk for CKD are available and should be part of the routine evaluation of patients with SLE with kidney involvement. Treatment decisions should be individualised, considering also patient preferences and their education, as emphasised by the patient research partners in the Task Force.

D. *Management aims to prevent progression of CKD and flares, address comorbidities, and improve health-related quality of life; both immunosuppressive therapy and nonimmune therapy, including kidney protection, are essential.*

The final overarching principle refers to the long-term goals of management. Prevention of CKD progression is crucial to avoid the long-term sequelae of kidney failure, including cardiovascular disease and infections [17]. To this end, prevention of LN flares is of utmost importance because with each flare, damage accumulates, and GFR decline may accelerate [22]. To achieve prevention of CKD progression, both immunosuppressive and nonimmune (kidney protective) treatments are needed. Immunosuppression aims to alleviate kidney inflammation and prevent irreversible damage, particularly in the early stages of LN. Long-term preservation of kidney function relies on kidney protective drugs and lifestyle measures that aim to maintain kidney function over time.

Individual recommendations

1. *Kidney biopsy is recommended in every patient with evidence of kidney involvement, especially in those with persistent proteinuria (≥0.5 g/24 h or urine protein-creatinine ratio ≥500 mg/g) (2b/B), glomerular haematuria (2b/C), and/or unexplained decrease in GFR (2b/C).*

This recommendation has remained unchanged from the 2019 update. Patients with SLE and any sign of kidney involvement (glomerular haematuria and/or cellular casts, proteinuria >0.5 g/d [or spot urine protein-to-creatinine ratio [UPCR] >500 mg/g], unexplained decrease in GFR) should be evaluated for a kidney biopsy. The 0.5 g/d proteinuria threshold was extensively debated among panelists, considering studies reporting significant rates of proliferative LN in patients with lower proteinuria [23,24], and increasing proteinuria trajectories in some patients who are initially below this threshold [25]. Nevertheless, the Task Force concluded that the decision to perform a kidney biopsy should consider all clinical factors (including extrarenal disease activity) and laboratory data (such as lupus serology) in each patient [26]; moreover, decision-making may differ in the case of the first diagnosis of LN versus a disease flare. Based on these deliberations, it was decided that the 0.5 g/d threshold should be kept as an indicative threshold to avoid potentially unnecessary biopsies, while not preventing biopsies at lower levels of proteinuria, if indicated. Histologic assessment of the kidney specimen should include elements of active and chronic disease (with computation of the National Institutes of Health [NIH] activity and chronicity indices), tubulointerstitial lesions with prognostic significance (interstitial inflammation or interstitial fibrosis and tubular atrophy) [27,28], as well as the presence of thrombotic microangiopathy (TMA, see also recommendation #11).

2. *Treatment should aim for optimisation (preservation or improvement) of kidney function within 3 months, accompanied by a reduction in proteinuria of at least 25% by 3 months (2b/C), 50% by 6 months (2a/B), and a UPCR target <700 mg/g by 12 months (1b/B), and as low as possible afterwards.*

This recommendation has no substantial changes from the 2019 update. No important new data have been added to the post hoc analyses of the MAINTAIN and Euro-Lupus Nephritis Trials, which established that proteinuria at 12 months represents the best predictor for long-term kidney outcome after 10 years [29−31]. Importantly, these targets have been validated in a single observational study [32]. Accordingly, the goals of 25% reduction by 3 months, 50% by 6 months (partial response), and an absolute UPCR value of <700 mg/g at 12 months remained unchanged; a change from the range of 500 to 700 mg (referred in the 2019 recommendations) was decided for the sake of simplification to provide a fixed threshold for the definition of response at 12 months rather than a range of UPr values, and because this threshold (ie, 700 mg) at 12 months has been associated with good long-term outcome. Complete renal response should be defined as UPCR <500 mg/g at any time point. These values represent suggestive thresholds, since there are patients who start with low-level proteinuria <1 g/d, and others who have severe nephrotic range proteinuria at baseline and may need more time to reach these targets. Together with proteinuria, stabilisation (if not improvement) of GFR to ≥80% of baseline value is desirable within the first 3 months to ensure that the patient is not deteriorating and in need of reevaluation of the treatment regimen. Notwithstanding its value in detecting kidney involvement, assessing urinary sediment for persistent glomerular haematuria after treatment initiation has limited independent prognostic value for long-term kidney function [31].

3. *For patients with active LN, IV pulse methylprednisolone is recommended (2b/C), followed by oral glucocorticoids gradually tapered to ≤5 mg/d prednisone-equivalent by 4 to 6 months (2b/C), and slowly withdrawn in patients with sustained complete renal response.*

Despite their side effects, glucocorticoids (GCs) remain an integral part of the armamentarium, especially in the early phase of treatment. Nevertheless, the optimal GC regimen and intensity remain unknown, as high-quality randomised studies comparing different regimens are lacking, and their efficacy and speed of action must be balanced against their well-established side effects. A recent meta-analysis of the control arms of RCTs found that a higher initial prednisone dose was associated with higher response rates, but also higher rates of serious infections and death at 6 months [33]. Whether the prednisone dose should be based on patient body weight (mg/kg) or not is also uncertain. A retrospective study of 206 patients with LN, using propensity score matching, found higher 1-year complete response rates in those starting with ≥40 mg/d compared with ≤30 mg/d, without an increased risk of GC-related damage in the higher-dose group [34]. Prednisone dosing based on weight remains the norm in paediatric practice.

The 2019 recommendations specified dose ranges for IV methylprednisolone pulses (total 500-2500 mg, based on disease severity), initial oral prednisone (0.3-0.5 mg/kg/d

for proliferative LN, 20 mg/d for class V), and tapering targets (≤7.5 mg/d by 3-6 months for proliferative LN, ≤5 mg/d by 3 months for class V) [4]. The present update recognises the need for individualisation of GC dosing, taking into consideration LN histology and other parameters (eg, extrarenal disease activity, risk for GC-associated toxicity) and, thus, has omitted specific doses from the statement. In general, pulse IV MP is recommended in the same range of 500 to 2500 mg cumulative dose, administered over 1 to 3 days. Regarding starting oral dose, a dose range of 0.3 to 0.7 mg/kg/d prednisone-equivalent for up to 4 weeks is typically recommended in class III or IV LN. The increase in the upper limit compared with the 2019 recommendations from 0.5 to 0.7 mg/kg/d, in the absence of new data, was decided following discussions among Task Force members, to allow more flexibility to treating physicians for selected cases of severe LN. In the AURORA trial of voclosporin, lower GC doses were used, starting from 25 mg/d, which represents the lowest recommended initial dose. For class V LN with subnephrotic range baseline proteinuria, less intense regimens of GC can be used. In patients who improve, oral GC should be gradually tapered to ≤5 mg/d by 4 to 6 months and ultimately withdrawn by 12 to 24 months. Importantly, GC reduction and withdrawal are now more feasible with combination therapies, including biologics. Specifically for paediatric patients, the recommended starting dose is 0.6 to 1.0 mg/kg/d. Weaning regimens for this age group may vary, but the overall aim to minimise the overall GC burden and duration of use remains paramount, in view also of longer-term impacts on childhood growth and development, as well as patient choice [35].

4. *For patients with active LN, especially those with poor prognostic factors, we recommend combination therapy of (a) mycophenolate or low-dose intravenous cyclophosphamide with belimumab (1b/A), or (b) mycophenolate with a calcineurin inhibitor (voclosporin or tacrolimus) (1b/A), or (c) mycophenolate with obinutuzumab (1b/A). Alternative regimens include single-agent immune therapy with either mycophenolate (1a/A) or low-dose intravenous cyclophosphamide (1a/A).*

This recommendation marks the most important change of the present update. Since the previous update in 2019, belimumab and voclosporin have been approved for the treatment of LN, following successful phase 3 RCTs [36,37]. The REGENCY phase 3 RCT of obinutuzumab, a humanised anti-CD20 monoclonal antibody, in combination with mycophenolate mofetil (MMF), also met its primary endpoint of complete renal response (UPCR <0.5, eGFR>85% of baseline, and no rescue therapy) at 76 weeks [38]. Details on the efficacy and safety of these RCTs are provided in the accompanying SLR manuscript [8].

After extensive deliberations, the Task Force reached a uniform consensus that, for most patients, initial treatment should include combination therapy—either belimumab with mycophenolic acid analogs (MPAA) or cyclophosphamide (CYC), or a calcineurin inhibitor (CNI) (tacrolimus or voclosporin) with MPAA, especially in those with poor prognostic factors (Table 2). Based on the successful RCT of obinutuzumab, obinutuzumab plus MPAA was considered an additional option. While patients with pure class V LN were not included in the REGENCY trial, the Task Force felt it could still be a viable option given its efficacy in mixed proliferative and membranous nephritis. Additionally, case reports have suggested the efficacy of obinutuzumab in primary membranous nephropathy, and an RCT is currently underway [39]. MPAA or low-dose CYC remain as final options in specific circumstances, explained below.

Table 2
Prognostic factors for (1) suboptimal response and development of chronic kidney disease and (2) kidney flares

Suboptimal response/progression to CKD	Flares
Reduced GFR at baseline (< 60 ml/min/m^2)	Nonadherence to treatment
Previous flare	Shorter duration of treatment (<3 years)
Nephrotic range proteinuria at baseline	Incomplete response following initial therapy
Hypertension at baseline	Ongoing extrarenal and serologic activity
Male sex	No use of HCQ
Increased chronicity index (>3, in the presence of activity)	Young age (<30 years)/male sex
Histologic evidence of crescents	Residual histologic activity (NIH AI ≥2) at repeat biopsy
Severe tubulointerstitial inflammation	

GFR, glomerular filtration rate; HCQ, hydroxychloroquine; NIH AI, National Institutes of Health Activity Index.

Important details and arguments that led to the current phrasing can be summarised as follows: (1) kidney involvement in SLE *by definition* constitutes a severe disease presentation associated with significant risk for CKD and its progression. Rates of complete response in RCTs remain low (between 20% and 30% at 6 months) indicating a major unmet need, and all 3 drugs (belimumab, voclosporin, and obinutuzumab), in combination with standard of care, have demonstrated superiority over standard of care alone in large phase 3 RCTs; (2) in the recommendation, no distinction is made between proliferative (class III and IV) and membranous (class V) LN classes, which marks a departure from previous recommendations [40,41]. As stated above, patients with pure class V LN were excluded from the phase III RCT of obinutuzumab. Moreover, even in RCTs that included class V LN, these patients are consistently underrepresented (~15% of the study population), and consequently, these studies were not designed or powered to detect treatment effects specifically in class V; (3) in addition to the different LN classes, the Task Force extensively debated the need to define additional patient subgroups for whom specific combination regimens may be preferred, based on post hoc analyses of the aforementioned RCTs. For example, belimumab was not found to be superior to standard of care in patients with baseline proteinuria >3 g/d [40]; in contrast, both voclosporin and obinutuzumab showed better efficacy in patients with high baseline proteinuria [38,42]. In BLISS-LN, only patients who received the combination of belimumab with MMF had better response rates over standard of care; however, only 25% of the study population received belimumab and CYC [36]. The Task Force decided to interpret the results of these post hoc subgroup analyses with caution, given that the individual studies were not designed to address efficacy in specific patient subgroups. Accordingly, a deliberate decision was taken to leave the treating physician with a variety of options, until more data become available, including from the real-life use of these drugs; (4) finally, the Task Force

recognises that there might be circumstances in which single-agent therapy with either MPAA or low-dose CYC is a reasonable option [43,44]. Such a decision may depend on disease characteristics (eg, a patient with an initial LN flare, low-grade proteinuria with preserved GFR, and mild histologic activity), ease of access to new drugs, as well as patient preferences. In this regard, response rates in observational studies tend to be higher than those reported in RCTs (especially in studies from Europe with a higher percentage of white patients) [45−47]. This notwithstanding, the 2025 EULAR update now recommends combination therapy for the majority of patients in healthcare settings with access to all therapeutic options.

Regarding the choice of combination therapy, certain safety considerations should be taken into account. In REGENCY, the obinutuzumab/MMF arm experienced a higher rate of infections than the placebo/MMF arm, mainly due to coronavirus disease 2019 (COVID-19)-related pneumonia (5.1% vs 0%, respectively) [38]. Of note, such a signal was not evident in the smaller phase 2 NOBILITY trial of the drug (carried out prior to the COVID-19 era) [48]. In this regard, the B-cell depleting agent rituximab has been associated with a higher risk of infections in patients on prednisolone >10 mg/d, those with serum IgG <6 g/L, or those with multimorbidity [49], as well as with an increased risk for COVID-19.[50] This underlines the need for effective preventive measures, including vaccinations (see recommendation #10). On the other hand, although the risk for nephrotoxicity seems to be lower with voclosporin than other CNIs, this class of drugs should be avoided (or used with caution) in patients with compromised kidney function (estimated GFR <30-45 ml/min/m^2) or substantial fibrosis in the kidney biopsy. Belimumab is not accompanied by significant safety issues.

Some specifications regarding paediatric disease should also be noted. To date, treatment of childhood-onset LN has generally followed the same principles of adult LN [9]. Regarding the newer drugs, belimumab (intravenous) has been approved for paediatric LN since 2022, despite the absence of prospective RCTs (the drug has only been tested in the phase 2 PLUTO trial in extrarenal SLE, with a nonstatistically significant favourable trend) [51]. By contrast, trials of voclosporin and obinutuzumab in children with LN are ongoing. Rituximab has been used in observational studies with good efficacy results [52].

5. *In patients with rapidly progressive glomerulonephritis, a short course (6-7 monthly pulses) of high-dose intravenous cyclophosphamide can also be considered (1a/A).*

Recommendation #5 refers to the specific subset of patients who present with rapidly progressive glomerulonephritis, ie, a rapid decline in kidney function accompanied by histologic evidence of extensive crescent formation (typically affecting >50% of the glomeruli). Apart from a post hoc analysis of the Aspreva Lupus Management Study in 32 patients with impaired kidney function at baseline, which found similar rates of response in terms of proteinuria and serum creatinine between MMF and high-dose intravenous CYC [43], no high-quality data are available for this subgroup of patients who are underrepresented in clinical trials and carry a poor prognosis. BLISS-LN, REGENCY, and AURORA RCTs excluded patients with low GFR at baseline (<30 in the former two and 45 ml/min/m^2 in AURORA, respectively); therefore, recommendations for these patients are not supported by high-level evidence. Although such patients can still be treated with the regimens mentioned in recommendation #4, a short course of high-dose intravenous CYC (modified traditional NIH regimen: 0.5-0.75 g/m^2 monthly for 6 months, total 6-7 pulses) is an additional option, since it remains the therapeutic regimen most studied in severe LN [53,54]. Combination with monthly pulse methylprednisolone has been shown to improve long-term renal outcome without adding toxicity [54]; therefore, the addition of monthly intravenous pulses of methylprednisolone (typically 1 pulse prior to CYC administration) is left to the physician's discretion [54,55]. Administration of monthly gonadotropin-releasing hormone analogs is recommended in premenopausal women who receive high-dose intravenous CYC to maximise the possibility of ovarian preservation.

6. *Following renal response, treatment should continue for at least 3 years (2b/B); patients initially treated with mycophenolate alone (1a/A) or in combination with (i) belimumab (1b/A), (ii) a calcineurin inhibitor (1b/A), or (iii) obinutuzumab (1b/A) should remain on these drugs; azathioprine (1a/A) or mycophenolate (1a/A) should replace cyclophosphamide for those initially treated with cyclophosphamide, alone or in combination with belimumab.*

This recommendation refers to what was formerly known as 'maintenance' or 'subsequent' therapy; clearly, the terms 'induction' and 'maintenance' are no longer suitable in cases where a combination regimen has been chosen from the start. The following principles refer to patients who have responded to initial therapy, as per the targets of treatment (recommendation #2). First, the total duration of therapy (also addressed in the next recommendation) should be individualised, but generally not be <3 years following response, especially for proliferative classes [56,57]. Second, long-term treatment should depend on the initially administered regimen. In this regard, the BLISS-LN RCT had a 2-year duration and a long-term extension phase, without major safety signals [36,58]. Advantages of the use of belimumab for long-term treatment of LN are its favourable safety profile, established also after over 10 years of real-life use in extrarenal SLE [59], and the reduction of renal flares shown in BLISS-LN [40]. Regarding combination treatment with MMF/CNI, there is a concern with potential nephrotoxicity associated with long-term CNI use. Importantly, the long-term AURORA-2 study extended the combination of MMF with voclosporin to 3 years and reported stable GFR levels throughout this period (although the dose of voclosporin for a proportion of the patients was reduced over time, which may have influenced its impact on GFR) [60]. Regarding combination with tacrolimus, data beyond 2 years are lacking [61]. Lastly, given its higher nephrotoxic potential compared to newer CNIs, cyclosporine is not preferred for long-term treatment. For obinutuzumab, the REGENCY RCT assessed the drug for 12 months (3 cycles every 6 months); thus, if obinutuzumab is to be used, it is currently recommended to follow this regimen, as longer treatment courses will require formal evaluation [38]. Finally, if CYC is used in the initial treatment regimen (either as monotherapy or in combination with belimumab), it should be replaced by MPAA or azathioprine (AZA), preferably the former, except if pregnancy is contemplated. As stated in recommendation #3, in patients who have responded, GC should be tapered to complete discontinuation, if possible,

by 12 months. For paediatric patients, there is no evidence to suggest that long-term immune treatment of LN should differ from the treatment of adults.

7. *In patients with sustained complete renal response, gradual withdrawal of immunosuppressive and/or biologic therapy should be considered after 3 years of therapy following response, taking into consideration the risk for flare (2a/B).*

This recommendation relates to the duration of treatment and, accordingly, optimal timing of immunosuppressive therapy withdrawal (excluding GC, covered in recommendation #3). Balancing the need to minimise long-term immunosuppression with the risk of flares after treatment tapering or withdrawal is crucial, as flares may harm the functional reserve of the kidney. In this regard, modifiable risk factors for flare, including nonadherence to treatment, shorter duration of treatment, ongoing extrarenal and serologic activity, no use of HCQ, as well as residual histologic activity despite seemingly clinical inactivity, should be considered (Table 2) [62]. The investigator-initiated WINLUPUS RCT compared the continuation versus withdrawal of immunosuppression in patients with LN who had received 2 to 3 years of therapy and were in stable disease (either complete renal remission with proteinuria ≤0.2 g/d, or partial with proteinuria ≤0.5 g/d, or stable and considered to be related to chronic damage, together with inactive urinary sediment and eGFR >90 mL/min/1.73 m² or ≥90% of baseline), for at least 1 year [57]. The study found higher rates of renal (and extrarenal) relapses in the withdrawal group (27.3% vs 12.5%). Notwithstanding this result, recent observational studies have reported satisfactory rates of flare-free immunosuppressive therapy withdrawal. Importantly, longer duration of treatment and remission prior to discontinuation, as well as continued use of HCQ, seem to be consistently associated with a lower risk for flare following withdrawal of immunosuppression [63,64]. The optimal duration of 'sustained' complete renal response remains unclear. A different approach may be followed in case of a new-onset vs flaring patients with LN, but sustained complete renal response should be considered as no shorter than 12 months in all circumstances [65]. As discussed below (recommendation #9), the decision to withdraw immunosuppressive treatment can be informed by the findings of repeat kidney biopsy in selected patients, given that residual histologic activity may predict a future relapse [66]; however, this may not be feasible in all settings. In view of this, many experts would treat patients with LN for at least 5 years before considering withdrawal of immunosuppression.

8. *For patients with persistently active or relapsing disease, switching among different immunosuppressive (2b/B) and/or biologic drugs (2b/B) and referral to experts is recommended.*

This recommendation refers to a disease not responding to initial immunosuppressive therapy and has resulted from merging 2 statements from the 2019 update. Prior to labelling disease as 'persistently active' or 'refractory', it is essential to first evaluate all possible causes of nonresponse. In this regard, assessment of adherence to treatment, including monitoring drug blood levels where available (eg, for MPAA or CNI), is important [67]. If adherence has been confirmed, a repeat biopsy may be considered to establish histologic activity (see also next recommendation).

If lack of response is attributed to persistently active disease, the expanded range of available therapies in recent years provides treating physicians with a variety of options. Any of the alternative regimens outlined in recommendation #4 can be tried. In cases of monotherapy with MPAA or CYC used as initial therapy, combination therapy should now be strongly considered. In 2019, a recommendation for rituximab was also made in cases of nonresponding disease, based on observational evidence [68]. With the recent success of obinutuzumab, it is reasonable that the latter is also an option. B-cell depletion with rituximab can be incomplete and less predictable in some cases, which affects response to the drug [69].

Ultimately, the choice of alternative regimen needs to be individualised and will depend on specific disease characteristics (eg, prominent proteinuria, wherein a CNI may be preferable). Given the complexity of the disease and available treatments, referral to or consultation with expert centres is strongly encouraged in nonresponding cases. Emerging evidence for the efficacy of CAR T-cells in cases of multirefractory SLE merits further exploration of this modality for cases of refractory kidney involvement [70].

9. *Repeat kidney biopsy should be considered, especially in cases of clinical uncertainty, to evaluate (i) response to treatment, (ii) worsening of kidney-specific laboratory tests, or (iii) contemplated withdrawal of immunosuppressive treatment (2b/B).*

This recommendation also does not bear significant changes from the 2019 recommendations. Despite being an invasive procedure, a repeat kidney biopsy provides information that cannot be inferred from clinical and laboratory parameters. Recent observational studies suggest that both activity and chronicity elements in repeat kidney biopsies may be more predictive of long-term GFR decrease or kidney failure, compared to baseline biopsies [71−73]. Thus, a second kidney biopsy should be considered if there is clinical uncertainty, including suboptimal response to treatment (to differentiate between ongoing activity and irreversible damage) and/or any worsening of kidney laboratory tests, as in the case of flare (to exclude nonlupus-related causes). A randomised trial, which tests the added value of repeat biopsy at 12 months in patients with LN, is currently underway [74]. An additional scenario, where a second kidney biopsy should be contemplated, is in patients in complete renal response after an adequate duration of immunosuppressive therapy (as defined above). As there is frequent discordance between clinical and histological remission [75], a repeat kidney biopsy may aid in the decision to withdraw immunosuppressive therapy. In this regard, an observational study in 32 patients showed that ongoing histological activity predicted a subsequent kidney flare after discontinuation of immunosuppression [66], while a retrospective study in patients with repeat biopsy-based management of immunosuppression reported lower rates of flares, when compared to historical controls [76]. Ultimately, the decision should be individualised and take patient preferences and local expertise into account.

10. *Nonimmune treatment with renin-angiotensin-aldosterone system blockade (for patients with persistent proteinuria or arterial hypertension) (5/D), sodium glucose transporter 2 inhibitors (for stable patients with persistent proteinuria or eGFR <60 ml/min/1.73m^2, or other risk factors for progressive CKD) (5/D), statins (based on cardiovascular risk levels) (5/D), and/or bone protective agents (5/D) is recommended.*

This recommendation refers to the second pillar of LN treatment, namely nonimmune treatment. It has resulted from

merging 6 different statements from the respective sections in the 2019 recommendations. Major changes include the following: (1) renaming this treatment to 'nonimmune', rather than 'adjunct'. As outlined also in the overarching principles, this change marks the realisation that nonimmune, kidney protective treatment is equally important as immune therapies to the long-term preservation of kidney function; (2) the inclusion of sodium glucose transporter 2 inhibitors (SGLT2is) in the therapeutic plan of LN. This class of drugs reduces kidney workload and has been shown to delay the progression of GFR decline in various forms of kidney disease [77,78]; of note, these studies also included patients with autoimmune disease-related CKD. Thus, although prospective data are currently lacking in SLE, the Task Force deemed these drugs to be offered to stable patients with persistent proteinuria or eGFR 20 to 60 ml/min/1.73m^2 (contraindicated in eGFR <20 ml/min) or other risk factors for progressive CKD. It remains unclear whether SGLT2i should be initiated at the outset or after several months of immunosuppressive therapy. However, the Task Force agreed that initiation should be delayed for at least 6 to 12 months until the disease stabilises with immunosuppression. Also, their use in paediatric patients is unclear, because they are not yet indicated in this age subgroup.

Furthermore, renin-angiotensin-aldosterone system (RAAS) blockade is recommended to control blood pressure levels (target <130/80 mm Hg) and also due to its antiproteinuric effects [79]. Antihypertensives with a different mechanism of action may be used if RAAS blockade is not tolerated, contraindicated (eg, hyperkalaemia, worsening azotaemia), or insufficient. Lifestyle kidney protective measures, including maintenance of a normal body weight, avoidance of smoking and nephrotoxic drugs (eg, nonsteroidal antiinflammatory drugs), and salt restriction, are of utmost importance [19]. Anticoagulation therapy should be temporarily administered in patients with nephrotic syndrome and severe hypoalbuminemia (albumin levels <2-2.5g/dL). For infection prevention due to the combined and prolonged immunosuppression, patients should be initially screened for possible latent or resolved infections (HBV, HCV, and tuberculosis) and receive prophylaxis when indicated. Patients should also be vaccinated with nonlive vaccines, including against influenza, *Streptococcus pneumoniae*, SARS-CoV-2, and herpes zoster [80]. Regarding protection from cardiovascular disease, patients should be assessed for their 10-year cardiovascular risk according to one of the available validated scores [81], based on lipid levels and presence of other cardiovascular risk factors, and therapy with statins should be considered accordingly [82]. Bone protection and prevention of osteoporosis should follow nonpharmacologic (exercise uptake, normal body mass index), as well as pharmacologic measures, according to individual fracture risk. Bisphosphonates should be used with caution in patients with reduced GFR.

11. *In patients with features of thrombotic microangiopathy (antiphospholipid syndrome nephropathy, thrombotic thrombocytopenic purpura-like, or complement mediated hemolytic uremic syndrome), GCs (including pulse IV methylprednisolone) (4/C), complement inhibitors (4/C), B-cell depleting agents (4/C), caplacizumab (4/C), plasma exchange (4/C), and/or anticoagulation (2b/C) should be considered.*

In recent years, the concept of TMA in SLE has evolved to encompass syndromes of various underlying aetiologies, ranging from classic thrombotic thrombocytopenic purpura (TTP), via complement-mediated hemolytic uremic syndrome (CM-HUS), to antiphospholipid syndrome (APS) nephropathy. These syndromes share the clinical picture of TMA, yet have distinct pathophysiologic mechanisms and may respond to different therapies. To this end, a diagnosis of TMA in the context of LN (histologic evidence of TMA, microangiopathic haemolytic anaemia and thrombocytopenia, involvement of the central nervous system) should prompt a diagnostic workup towards the underlying pathophysiology, in order to guide targeted treatment. The presence of low ADAMTS13 activity confirms a diagnosis of TTP, wherein plasma exchange is recommended, followed by immunosuppressive treatment for LN. Caplacizumab, a bivalent variable domain-only immunoglobulin fragment against von Willebrand factor approved for the treatment of acquired TTP [83], can be considered in nonresponding TTP patients, although data in patients with SLE are currently limited to a few case reports. The use of complement inhibitors (eculizumab and ravulizumab) should be considered if TTP has been ruled out and activation of the complement pathway remains as the suspected underlying aetiology (CM-HUS). Accumulating observational data suggest that complement inhibitors may be particularly effective in the subset of patients with CM-HUS with significant kidney injury [84,85]. Finally, anticoagulation is recommended in the presence of TMA accompanied by positive antiphospholipid antibodies, especially at high titres, which establishes the diagnosis of APS nephropathy [86].

12. *In patients with inactive nephritis and whose extrarenal manifestations are adequately controlled, pregnancy may be planned after preconception counselling, initiation of pregnancy-compatible medications, and regular multidisciplinary assessments (1b/A).*

The 2019 recommendations included a section with 6 statements regarding pregnancy in patients with LN, including optimal timing, compatible medications, use of aspirin, and need for multidisciplinary assessment. Since no significant new data have emerged following the previous update, the section has now been merged into a single recommendation, without major contextual changes. EULAR has issued specific recommendations for family planning in SLE, including pregnancy and lactation [87]. A history of kidney involvement poses significant risks for mother and foetus; thus, the value of preconception counselling cannot be overemphasised. Active LN, especially with impaired kidney function, is a relative contraindication for pregnancy, which should be postponed until the disease is controlled and stable for at least 6 months. Inactive disease would ideally necessitate a kidney biopsy to show the absence of histologic activity, but this is not available in most circumstances. The ideal clinical scenario would be a patient with normal kidney function and blood pressure and a UPCR<500 mg/g, but this may often not be achievable. To this end, pregnancy should be contemplated only in patients with stable LN and following risk stratification based on CKD stage [88].

Pregnancy-compatible medications include GC, AZA, and CNI, which should be continued throughout pregnancy and lactation, along with HCQ (currently, there is insufficient evidence regarding the safety of voclosporin during

pregnancy/lactation) [89]. Blood pressure should be controlled without the use of RAAS inhibitors, which are teratogenic in the first trimester. The use of low-dose aspirin is recommended because a history of LN increases the risk of preeclampsia. Immunosuppressive drugs, which are contraindicated in the first trimester (eg, MPAA, CYC), may be considered in the second or third trimester for life-threatening disease; B-cell depleting agents should be avoided in the third trimester due to possible neonatal hypogammaglobulinemia and compromised response to vaccinations. Finally, pregnancy in patients with a history of kidney involvement should be monitored by a multidisciplinary team, including an obstetrician with expertise in the disease and high-risk pregnancies.

13. *All methods of kidney replacement therapy can be used in patients with SLE; in those with clinically inactive extrarenal disease for at least 6 months, transplantation (including living donor and preemptive transplantation) should be considered (2b/C).*

The final recommendation has also remained essentially unchanged from the 2019 update. Once a patient with LN reaches kidney failure, all methods of kidney replacement therapy can be used. Preemptive transplantation is associated with better 10-year kidney survival rates [90,91]; however, only a small proportion of patients are currently offered this possibility. Transplantation should not be delayed in patients who are in remission or sustained low extrarenal disease activity (eg, sustained lupus low disease activity state) [92]. Regarding haemodialysis and continuous peritoneal dialysis, a meta-analysis showed no difference in the risk for disease flares, all-cause infections, and mortality, although a higher risk for all-cause cardiovascular events was evident for haemodialysis (relative risk 1.44) [93]. Recent data from the ERA registry suggest that the prognosis of patients with lupus receiving kidney replacement therapies has improved over time, with better 10-year patient survival rates, which are similar to patients who required kidney replacement therapies for other causes of kidney failure (HR 1.11) [94].

The same principles apply in paediatric patients. Yet, a recent US retrospective cohort study suggested that children and adolescents with LN on dialysis may carry a higher risk for adverse outcomes, including hospitalisation, and are less likely to receive kidney transplantation compared to children with other causes of kidney failure [95].

Construction of quality indicators

We chose the 3 recommendations with the best balance between feasibility and impact on quality of care to construct respective quality indicators (Supplementary Table 1). These were recommendations #4, 6, and 10 and are the ones that focus on immune (#4,6) and nonimmune (#10) treatment of kidney involvement in SLE. The proposed quality indicators are shown in Table 3, and their implementation will be tested following publication of the recommendations.

DISCUSSION

Following years of failures of clinical trials, the recent pace of therapeutic advances for patients with SLE and kidney involvement has accelerated [96]. Herein, we gathered a multidisciplinary and multinational panel of LN experts across 3 continents to ensure the widest possible representation and broadest expertise. To emphasise the concept that kidney involvement in SLE is a manifestation of a multisystem disease, even when it dominates the clinical picture, the project was entitled ‘Recommendations for the management of SLE with kidney involvement’, rather than ‘LN’.

A major modification of the present update compared to the 2019 EULAR-ERA/EDTA recommendations is the drastic reduction in the total number of individual recommendations, in line with the current EULAR SOPs. The consolidation of the statements to 4 overarching principles and 13 individual

Table 3
EULAR recommendations for the management of patients with systemic lupus erythematosus and kidney involvement—2025 update: Quality Indicators

		When to measure	How to measure
QI 1	Immune therapy If a patient with SLE has active nephritis, THEN combination therapy should be administered—especially if poor prognostic factors are present—consisting of either (1) mycophenolate or low-dose intravenous cyclophosphamide with belimumab, (2) mycophenolate with a calcineurin inhibitor (voclosporin or tacrolimus), or (3) mycophenolate with obinutuzumab. Alternative regimens include therapy with either mycophenolate or low-dose intravenous cyclophosphamide for selected patients.	At the initiation of immunosuppressive treatment	Clinical audit
QI 2	Duration of therapy If a patient with nephritis responds to initial treatment, THEN treatment should continue for at least 3 years, based on the initial regimen. Patients initially treated with mycophenolate alone or in combination with (1) belimumab, (2) calcineurin inhibitor, or (3) obinutuzumab[a] should remain on these drugs. Mycophenolate or azathioprine should replace cyclophosphamide for those initially treated with cyclophosphamide, alone or in combination with belimumab.	Month 6 onwards, following initiation of immunosuppressive treatment	Clinical audit
QI 3	Nonimmune therapy If a patient with SLE has kidney involvement, THEN nonimmune treatment with RAAS blockade (for patients with persistent proteinuria or arterial hypertension), SGLT2 inhibitors (for stable patients with persistent proteinuria or eGFR <60 ml/min/m^2, or other risk factors for progressive CKD), statins (based on cardiovascular risk levels), and/or bone protective agents should be given, as appropriate.	Month 6 onwards following initiation of immunosuppressive treatment[b]	Clinical audit

[a] Obinutuzumab was used for a maximum of 1 year (52 weeks) in the REGENCY trial; longer courses await further evaluation.
[b] This QI spans the whole period of treatment. The 6-month time point is an indicative starting point, when adherence to this recommendation should be evaluated.

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium glucose transporter 2.

recommendations attempts to summarise the major directions in a simple, yet not simplistic, way, to facilitate the dissemination and implementation of the recommendations in clinical practice. These major pillars of management are summarised in the Figure. The accompanying text of the recommendations will provide the reader with a more thorough understanding of the supporting data behind each statement. In this regard, no significant changes have been made regarding indications for a diagnostic kidney biopsy, goals of treatment, issues of pregnancy, and management of LN-kidney failure, and the respective recommendations have remained essentially unchanged. Little progress has also been made regarding the optimal use of GC in LN, both in terms of starting dose and tapering strategies. For this reason, apart from a universal recommendation for IV methylprednisolone pulses, the recommendations provide a range of starting doses, based on physician discretion, as well as a general guidance that, in patients who respond, GC should be withdrawn within the first 1 to 2 years.

The current update marks a paradigm shift for the immunosuppressive treatment of patients with SLE with kidney involvement. EULAR now recommends an initial combination regimen of MPAA with belimumab, a CNI, or obinutuzumab (plus GC) for all patients with active LN, especially those with adverse risk factors at baseline. This recommendation comes only 1 year after the publication of the EULAR recommendations for the management of general SLE, wherein it was stated that combination regimens 'should be considered' for all patients. Therein, single-agent therapy with either MPAA or CYC was still recommended. This gradual shift in phrasing was the combination of both evidence-based (superiority of combination treatments over monotherapy in high-quality phase 3 RCTs) and the opinion of experts within the Task Force. Indeed, combination treatments are being increasingly used in clinical practice and tend to become standard of care early, at least in healthcare settings with access to these drugs. Nevertheless, single-agent therapy with drugs with an established record in LN is still an option, especially in the absence of poor prognostic factors and in countries with limited access to new therapies.

B-cell depletion has long been considered an attractive therapy for kidney involvement in SLE. Despite the failed LUNAR trial [97], rituximab has been extensively used mainly in refractory cases of LN. The recent successful trials of obinutuzumab, which induces a more consistent depletion of B-cells compared to rituximab, have reignited interest in B-cell depletion as first-line treatment in LN. Although there has been extensive experience with obinutuzumab in hematologic malignancies, real-life experience in LN is limited. The potentially increased risk for infections that accompanies B-cell depleting therapies may be mitigated in part by decreased doses of GC in current regimens and the availability of effective vaccines. Rituximab may still be considered if other options have failed and obinutuzumab is unavailable. The potential of deep B-cell depletion in SLE is also supported by the recent successful case series of both CAR T-cells and bispecific T-cell engagers, but these treatments await confirmation in larger randomised trials [70,98].

The second important shift in the current recommendations is the upgrading of the importance of kidney protective treatment for the long-term management of LN, reflected both in the overarching principles and recommendation #9. For years, immunosuppressive treatment has monopolised interest (and

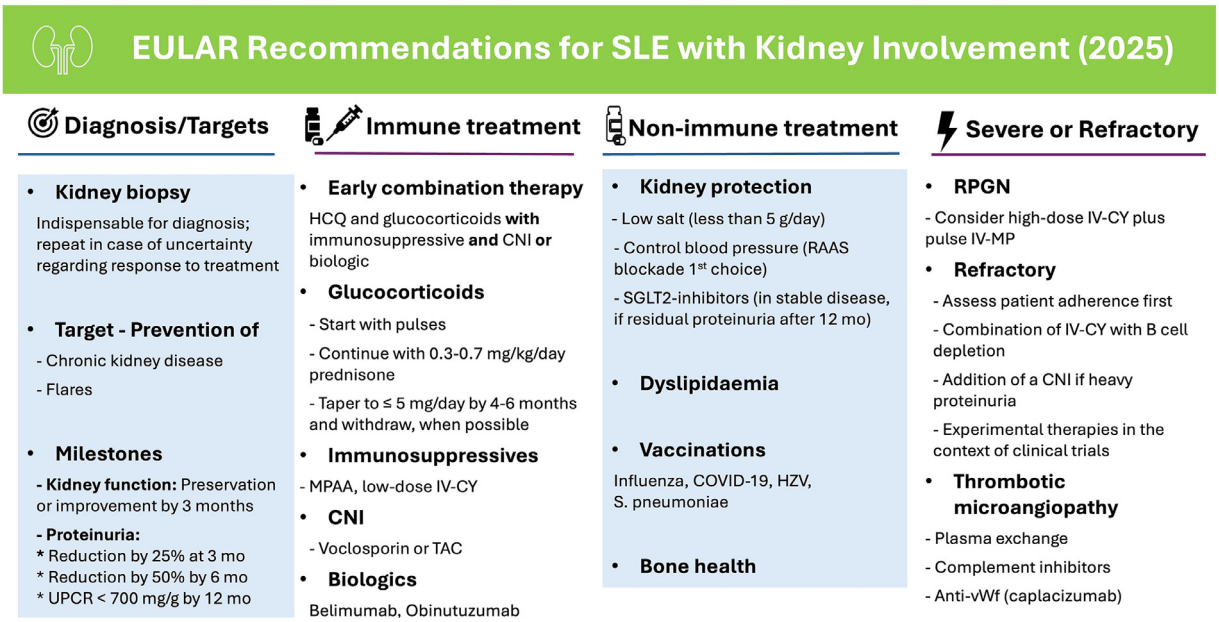
EULAR Recommendations for SLE with Kidney Involvement (2025)
Diagnosis/Targets
• Kidney biopsy
Indispensable for diagnosis; repeat in case of uncertainty regarding response to treatment
• Target - Prevention of
- Chronic kidney disease
- Flares
• Milestones
- Kidney function: Preservation or improvement by 3 months
- Proteinuria:
* Reduction by 25% at 3 mo
* Reduction by 50% by 6 mo
* UPCR < 700 mg/g by 12 mo
Immune treatment
• Early combination therapy
HCQ and glucocorticoids with immunosuppressive and CNI or biologic
• Glucocorticoids
- Start with pulses
- Continue with 0.3-0.7 mg/kg/day prednisone
- Taper to ≤ 5 mg/day by 4-6 months and withdraw, when possible
• Immunosuppressives
- MPAA, low-dose IV-CY
• CNI
- Voclosporin or TAC
• Biologics
Belimumab, Obinutuzumab
Non-immune treatment
• Kidney protection
- Low salt (less than 5 g/day)
- Control blood pressure (RAAS blockade 1st choice)
- SGLT2-inhibitors (in stable disease, if residual proteinuria after 12 mo)
• Dyslipidaemia
• Vaccinations
Influenza, COVID-19, HZV, S. pneumoniae
• Bone health
Severe or Refractory
• RPGN
- Consider high-dose IV-CY plus pulse IV-MP
• Refractory
- Assess patient adherence first
- Combination of IV-CY with B cell depletion
- Addition of a CNI if heavy proteinuria
- Experimental therapies in the context of clinical trials
• Thrombotic microangiopathy
- Plasma exchange
- Complement inhibitors
- Anti-vWf (caplacizumab)

Figure. Overview of the treatment strategy for SLE with kidney involvement and its key targets, milestones, and pillars of therapy. Early kidney biopsy and early initiation of combination treatment, especially for patients with adverse renal factors, are of paramount importance. Patients with adverse prognostic factors are more likely to receive more intense therapy for longer periods of time. Aggressive glucocorticoid tapering to a minimal prednisone equivalent of ≤5 mg/d or discontinuation, along with immunosuppressive and biologic therapy for at least 3 years after achieving a complete response, is recommended. Background use of antimalarials, immunisations, and kidney protection with control of blood pressure and antiproteinuric agents for patients with residual proteinuria after 6 to 12 months are additional measures to ensure optimal long-term outcomes. Doses of drugs: HCQ: 5 mg/kg/d (up to 400 mg/d); MPAA, mycophenolate mofetil 1-1.5 g twice daily—mycophenolate sodium 720-1080 mg twice daily; low-dose IV-CY: 500 mg on weeks 0, 2, 4, 6, 8, and 10; voclosporin: 23.7 mg twice daily; TAC: 0.05 to 0.1 mg/kg/d initially, titrated to target blood concentration 4-6 ng/ml 12 hours after dose; belimumab: SC 400 mg weekly for 4 doses, then 200 mg once weekly or IV 10 mg/kg every 2 weeks for the first 3 doses and every 4 weeks thereafter; obinutuzumab: 1000 mg on days 1 and 15—readministration at 6 months. CNI, calcineurin inhibitor; CsA, cyclosporine A; HCQ, hydroxychloroquine; HZV, herpes zoster; IV-CYC, intravenous cyclophosphamide; MPAA, mycophenolate acid analogs; RAAS, renin-angiotensin-aldosterone system; RPGN, rapidly progressive glomerulonephritis; SGLT2, sodium glucose transporter 2; TAC, tacrolimus; UPCR, urine protein-to-creatinine ratio; vWf, von Willebrand factor.

research) as the single most important pillar of treatment. The recent advent of new drugs with kidney protective properties over a spectrum of diseases associated with CKD (SGLT2i, mineralocorticoid receptor antagonists, endothelin receptor antagonists) has helped to realise that prevention of CKD occurrence and progression—the ultimate goal of treatment in LN—is best served by the combination of immunosuppression and kidney protection. This two-arm therapy illustrates the crucial importance of multidisciplinary management and monitoring of these patients, expressed also as a wish by the patient representatives in the Task Force. Nephrologists are typically more familiar with the use of kidney protective drugs and advice on respective lifestyle measures, whereas rheumatologists approach lupus patients from the perspective of a systemic disease and focus also on extrarenal manifestations.

Recommendations provide a framework for the state-of-the-art management of a disease, yet their implementation in real-life clinical practice is often suboptimal for a variety of reasons [99]. Following the 2019 EULAR recommendations for the management of general SLE, we created a list of quality indicators [100]; these were validated both internally, as well as independently in a cohort of patients in relation to their quality of life [101]. EULAR now specifies in its SOPs that specific measures should be taken following the publication of a set of recommendations, to maximise the possibility of their implementation [102]. To this end, we have constructed 3 key quality indicators—balanced for feasibility and impact—in tabular form based on the current recommendations to serve as a checklist for physicians who treat patients with SLE with kidney involvement. Finally, an agenda with questions for future research is shown in Table 4.

In summary, we have updated the EULAR recommendations for SLE with kidney involvement, in view of significant recent advances, to provide physicians with evidence- and eminence-based guidance. Together with the recently published KDIGO recommendations [103] and the American College of Rheumatology guidelines [104], physicians will now have more evidence to base their therapeutic decisions for this challenging manifestation of lupus.

Table 4
Research agenda in SLE with kidney involvement

Diagnosis
- Atypical presentations: podocytopathies and pauci-immune lupus nephritis, other forms
- Validated definition of kidney flares

Therapies and disease monitoring
- Early disease and therapeutic window of opportunity
- Mechanisms of severe refractory disease
- B-cell depleting therapies, including CAR-T-cells and bispecific T-cell engagers
- Combination of B-cell depleting with B- or T-cell–modifying therapies
- Improvement of complete renal response rates and deep flare-free remission
- 'Add-on' therapies to achieve deep remission
- Imaging for kidney fibrosis
- Duration and withdrawal of therapy
- Protocolised repeat biopsies: value of early vs late repeat biopsy
- Efficacy of different treatments for various forms of SLE-associated TMA with kidney involvement
- Drug level monitoring and improvement of compliance with treatment
- Nonimmune mechanisms in the progression of kidney disease, such as hypertension, obesity, and dyslipidaemia
- Optimal timing of SGLT2i initiation in SLE with kidney involvement

Pathophysiology and biomarkers
- Biomarkers for liquid biopsy
- Risk stratification of subgroups based on molecular signatures or other biomarkers
- Noninvasive means to classify the types of SLE with kidney involvement and activity status (urine cells, omics, etc)
- Renal progenitor cells and their proliferation in SLE with kidney involvement
- Kidney repair in SLE with kidney involvement

Lupus Nephritis Trial Design
- Better definition of clinical trial endpoints
- Optimisation of 'standard-of-care' (background) treatments
- Trials on class V lupus nephritis

CAR-T-cells, chimeric antigen receptor; SGLT2i, sodium glucose transporter 2 inhibitor; TMA, thrombotic microangiopathy.

Competing interests

AF reports lecture or consultancy fees from AstraZeneca, GSK, Boehringer Ingelheim, Genesis Pharma, Pfizer, AbbVie, and Eli Lilly. MK reports honoraria and/or consulting fees from GSK, participation in advisory boards from GSK, AstraZeneca, and Amgen. HJA reports lecture or consultancy fees from AstraZeneca, GSK, Novartis, Boehringer Ingelheim, Roche, and Otsuka. JA reports no direct conflict of interest, but LUPUS EUROPE is funded by grants or donations from Pharmaceutical Companies (Amgen/Horizon, AstraZeneca, Biogen, BMS, Galapagos, GSK, Viatris, Johnson & Johnson, Merck, Novartis, Otsuka, Roche, and UCB); none of which exceeds 25% of total funds collected, and none having a say on the content of studies or work by LUPUS EUROPE. MA reports advisory boards and/or lectures for AstraZeneca, GSK, Otsuka, and Roche. RF reports consulting fees from Genentech, GSK, Aurinia, Alexion, AstraZeneca, BMS, Novartis, Kyverna, and Boehringer Ingelheim. FH reports research grants from GSK and Roche and consulting/advisory fees from Neovacs, GSK, AstraZeneca, Eli Lilly, Idorsia, Otsuka, Biogen, and Galapagos. AK reports consultant fees from GSK, Vifor, Novartis, Otsuka, and Roche and honoraria from Pfizer, AstraZeneca, GSK, Novartis, Vifor, Otsuka, and Boehringer Ingelheim. AM reports advisory and speaker fees from GSK, Pfizer, Kezar, Roche, BMS, Novartis, and Biogen. AVM is funded by the National Institute for Health and Care Research (NIHR) Manchester Biomedical Research Centre (BRC) (NIHR203308) (the views expressed are those of the author and not necessarily those of the NIHR or the Department of Health and Social Care) and reports grant support from UCB and Janssen. GM reports speaker fees from GSK, Otsuka, and Vifor. IP reports research funding and/or honoraria from Amgen, AstraZeneca, Aurinia, BMS, Elli Lilly, Gilead, GSK, Janssen, Novartis, Otsuka, and Roche. YT reports speaking fees and/or honoraria from Chugai, UCB, AbbVie, AstraZeneca, Eli Lilly, Behringer-Ingelheim, GSK, Eisai, IQVIA, Daiichi-Sankyo, Otsuka, Taisho, Gilead, and BMS. GB has received honorary fees from GSK, AbbVie, AstraZeneca, UCB, Lilly, Otsuka, and Novartis and grants from MSD, AstraZeneca, and GSK. DTB reports unrestricted investigational grants from GSK and honoraria/consulting fees from GSK, AstraZeneca, AbbVie, Aenorasis, and Pfizer. The remaining authors declare no conflicts of interest.

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